transfer immunotherapy. Clin. Cancer Res. *17*, 4550–4557.

9. Dudley, M.E., Wunderlich, J.R., Yang, J.C., Sherry, R.M., Topalian, S.L., Restifo, N.P., Royal, R.E., Kammula, U., White, D.E., Mavroukakis, S.A., et al. (2005). Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J. Clin. Oncol. *23*, 2346–2357.

10. Guillaume, T., Gaugler, B., Chevallier, P., Delaunay, J., Ayari, S., Clavert, A., Rialland, F., Le Gouill, S., Blin, N., Gastinne, T., et al. (2012). Escalated lymphodepletion followed by donor lymphocyte infusion can induce a graft-versus-host response without overwhelming toxicity. Bone Marrow Transplant. *47*, 1112–1117.

11. Onea, A.S., and Jazirehi, A.R. (2016). CD19 chimeric antigen receptor (CD19 CAR)-redirected adoptive T-cell immunotherapy for the treatment of relapsed or refractory B-cell Non-Hodgkin's Lymphomas. Am. J. Cancer Res. *6*, 403–424.

Nanotechnology in Wound Care: One Step Closer to the Clinic

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The burden of the management of problematic skin wounds characterized by a compromised skin barrier is growing rapidly. Almost six million patients are affected in the US alone, with an estimated market of $25 billion annually.[1] In response, many interdisciplinary strategies are being developed to treat skin wounds. Traditional techniques aim to simply cover the wound without playing any active role in wound healing. However, nanotechnology-based solutions are being used to create multipurpose biomaterials, not only for regeneration and repair, but also for on-demand delivery of specific molecules.[2,3] In fact, nanotechnology-based biomaterials can be tailored for specific types of wounds, for example, to prevent the deterioration of chronic wounds.[4] In this issue of *Molecular Therapy*, Li et al.[5] report the development of a new delivery platform based on lyophilized keratinocyte-targeted lipid nanoparticles to facilitate keratinocyte-specific delivery of oligonucleotides to wounds. They further report the application of the system within a hydrogel on the wound and propose translational advantages and a longer shelf-life in wound management. Although liposomes have been extensively used for nanomaterials targeting cancer therapeutics, this work is among the first attempts to target lipid nanoparticles in a non-cancer health care application.

The human skin can act as a drug delivery route itself, minimizing the first-pass risk through the liver, which greatly reduces the bioavailability of drugs.[6] Although very small nanoparticles may directly penetrate the stratum corneum of the skin, larger nanoparticles (>10 nm) access the skin via hair follicles (which have a very low density in the skin [32 follicles/cm^2]), indicating that nanoparticles designed for delivery purposes across the skin should be very small.[7,8] In full-thickness skin defects, the skin barrier is partially compromised, but, due to the abundance of inflammatory cells, phagocytic clearance of nanoparticles is another challenging issue.[9,10] Therefore, innovative surface modification of nanoparticles might allow selective evasion of phagocytic clearance by distinct macrophage phenotypes.[11] The study by Li et al.[5] addresses this concern, offering an advanced selective delivery system of lyophilized keratinocyte-targeted nanocarriers loaded with locked nucleic acid (LNA)-modified anti-microRNAs (miRs) that significantly increase Dicer expression and downregulate p21$^{Waf1/Cip1}$ expression. The authors suggested that the proposed formulation, when applied to the skin, could penetrate the stratum corneum to specifically target keratinocytes for cargo delivery. Dicer is an RNAase-III enzyme that plays a critical role in re-establishing the barrier function of the skin. It is responsible for the biogenesis of key miRs, including miR-20a, miR-93, and miR-106b. These miRs play pivotal roles in establishing the barrier function of the regenerating skin by inhibiting the expression of p21$^{waf1/Cip1}$.

The endocytic pathway is the most important uptake system for biological molecules.[12] The entrapped agents in endosomes are further degraded in the lysosome. Therefore, a major drawback in realizing an effective wound healing process is to improve endosomal escape through a cytosolic delivery of therapeutic agents.[13] As noted, the designed lyophilized keratinocyte-targeted nanocarriers employed DOTAP/DODAP combination pH-responsive lipid components to improve endosomal escape. These nanocarriers possess near-zero surface

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charges and quickly react to the endosoal pH drop by boosting surface charges to +15 mV so as to stimulate efficient endosomal release.

Another trick in the proposed system is the neutral surface charge of the nanocarriers, enabling them to evade clearance by non-targeted immune cells in the wound area. It has been previously reported that the surface charge of nanoparticles can possibly act as a confounding factor when intending to target specific cells.[14] Collectively, these results demonstrate that it is possible to increase the clinical success in full-thickness skin defects where the proposed delivery system is sufficiently effective to meet particular clinical needs.

As with any advance, this study raises intriguing questions. This research sheds light on the potential of surface-modified nanoparticles for target-specific applications in wound repair, suggesting the next generation of applicable targeting platforms for further clinical use. Due to the use of lyophilized powders in the hydrogel system, the shelf-life of the final product is extended, which is a critical factor for market application. Another advantage of the lyophilized keratinocyte-targeted nanocarriers is that all the components in the formulation have been previously approved by US Food and Drug Administration (FDA) for human use, shortening the way toward clinical testing.

It is anticipated that this idea and the advent of innovative techniques and strategies in nanotechnology and cellular biology could result in significant future advances in wound management. For this particular design, when topically applied to the skin, it can efficiently move across the stratum corneum to explicitly target keratinocytes for cargo delivery. Although this strategy suggests a simple and scale-up-friendly and cell-specific delivery platform for wound care applications, it needs further investigation in the way of clinical testing, and many critical questions have to be answered before it can be successfully advanced.

CONFLICTS OF INTEREST

M.M. is an inventor on related topics to directed evolution.

REFERENCES

1. Frykberg, R.G., and Banks, J. (2015). Challenges in the treatment of chronic wounds. Adv. Wound Care (New Rochelle) *4*, 560–582.
2. Zarrintaj, P., Moghaddam, A.S., Manouchehri, S., Atoufi, Z., Amiri, A., Amirkhani, M.A., Nilforoushzadeh, M.A., Saeb, M.R., Hamblin, M.R., and Mozafari, M. (2017). Can regenerative medicine and nanotechnology combine to heal wounds? The search for the ideal wound dressing. Nanomedicine (Lond.) *12*, 2403–2422.
3. Kargozar, S., and Mozafari, M. (2018). Nanotechnology and Nanomedicine: Start small, think big. Mater Today *5*, 15492–15500.
4. Andreu, V., Mendoza, G., Arruebo, M., and Irusta, S. (2015). Smart dressings based on nanostructured fibers containing natural origin antimicrobial, anti-inflammatory, and regenerative compounds. Materials (Basel) *8*, 5154–5193.
5. Li, J., Ghatak, S., El Masry, M.S., Das, A., Liu, Y., Roy, S., Lee, R.J., and Sen, C.K. (2018). Topical Lyophilized Targeted Lipid Nanoparticles in the Restoration of Skin Barrier Function following Burn Wound. Molecular Ther. *26*, this issue, 2178–2188.
6. Prausnitz, M.R., and Langer, R. (2008). Transdermal drug delivery. Nat. Biotechnol. *26*, 1261–1268.
7. Prow, T.W., Grice, J.E., Lin, L.L., Faye, R., Butler, M., Becker, W., Wurm, E.M., Yoong, C., Robertson, T.A., Soyer, H.P., and Roberts, M.S. (2011). Nanoparticles and microparticles for skin drug delivery. Adv. Drug Deliv. Rev. *63*, 470–491.
8. Alvarez-Román, R., Naik, A., Kalia, Y.N., Guy, R.H., and Fessi, H. (2004). Skin penetration and distribution of polymeric nanoparticles. J. Control. Release *99*, 53–62.
9. Gordon, S. (2016). Phagocytosis: an immunobiologic process. Immunity *44*, 463–475.
10. Milan, P.B., Lotfibakhshaiesh, N., Joghataie, M.T., Ai, J., Pazouki, A., Kaplan, D.L., Kargozar, S., Amini, N., Hamblin, M.R., Mozafari, M., and Samadikuchaksaraei, A. (2016). Accelerated wound healing in a diabetic rat model using decellularized dermal matrix and human umbilical cord perivascular cells. Acta Biomater. *45*, 234–246.
11. Mohammadi, M.R., Nojoomi, A., Mozafari, M., Dubnika, A., Inayathullah, M., and Rajadas, J. (2017). Nanomaterials engineering for drug delivery: a hybridization approach. J. Mater. Chem. B Mater. Biol. Med. *5*, 3995–4018.
12. Varkouhi, A.K., Scholte, M., Storm, G., and Haisma, H.J. (2011). Endosomal escape pathways for delivery of biologicals. J. Control. Release *151*, 220–228.
13. Lönn, P., Kacsinta, A.D., Cui, X.-S., Hamil, A.S., Kaulich, M., Gogoi, K., and Dowdy, S.F. (2016). Enhancing endosomal escape for intracellular delivery of macromolecular biologic therapeutics. Sci. Rep. *6*, 32301.
14. Fröhlich, E. (2012). The role of surface charge in cellular uptake and cytotoxicity of medical nanoparticles. Int. J. Nanomedicine *7*, 5577–5591.